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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: )

A. Skoultchi, et al. )

Serial No.: 08/102,390 )

Filed: August 5, 1993 )

For: PRODUCTION OF )  
PROTEINS USING HOMOLOGOUS )  
RECOMBINATION )

Art Unit: 1804

Examiner:

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INFORMATION DISCLOSURE STATEMENT

Hon. Commissioner of  
Patents and Trademarks  
Washington, D.C. 20231

Sir:

This Information Disclosure Statement and form PTO-1449 are being submitted for the above-identified patent application.

The Applicants hereby submit patents, publications, or other information of which they are aware, which they believe may be material to the examination of the above referenced application and in respect to which there may be a duty to disclose in accordance with 37 CFR 1.56.

In accordance with 37 CFR 1.97(b), the filing of this Information Disclosure Statement shall not be construed as a representation that a search has been made, or that no other material information as defined by 37 CFR 1.56 exists. The disclosure statement herein does not constitute an admission that any patent, publication or other information cited alone

or in combination constitutes prior art for the invention under 35 U.S.C. §102 or §103.

LISTING AND EXPLANATION OF INFORMATION ITEMS

A list of patents and publications is set forth on the attached Form PTO-1449. The list is divided into U.S. Patents, Foreign Published Applications or Patents, and Other Printed Publications so that document identification data prescribed in 37 CFR 1.98 may be conveniently set forth. A description of each information item is provided.

U.S. Patents:

Publication AA, U.S. Patent No. 4,656,134 by Ringold, issued April 7, 1987, describes a method for enhancing production and expression of a DNA sequence of interest by transforming a eukaryotic auxotrophic host cell with DNA units containing an amplifiable structural gene joined to a DNA sequence of interest, and propagating the transformants under selective conditions to achieve amplification of the desired sequence.

Foreign Published Applications or Patents:

Publication AB, PCT application publication No. WO 91/09955 by Chappel, published July 11, 1991, was filed and published after the filing date of the grandparent application of the present application, U.S. Serial Number 07/432,069, filed November 6, 1989. This publication describes a process for modifying the expression characteristics of a gene naturally present within the genome of a cell line or cloned microorganism. In particular, the process involves identification of the resident gene encoding the desired product and insertion of an appropriate regulatory and/or

amplification gene by homologous recombination, in order to obtain expression of the desired product.

Publication AC, PCT application publication No. WO 93/09222 by Selden et al., published May 13, 1993, was filed and published after the filing date of the parent application of the present application, U.S. Serial Number 07/787,390, filed November 4, 1991. This publication describes a method for introducing exogenous DNA into somatic cells through homologous recombination, to activate an endogenous gene, thereby enhancing cellular expression of a desired product.

Other Printed Publications:

The Applicant is aware of the printed publications listed on form PTO-1449 which may be material to the examination of the referenced application.

These publications are discussed in the specification of the above-identified application as follows: Publications AD through AI are cited on page 2 of the application. Publications AJ and AK are cited on page 3 of the application. Publication AL is cited on page 12 of the application. Publication AD is cited again on page 10; Publication AK is cited again on page 14; and Publication AG is cited again on page 16.

Publications not discussed in the specification are as follows:

Publication AM, Kamarck et al. (1987) Proc. Natl. Acad. Sci. USA 84:5350-5354, reports the use of genomic DNA and mRNA from the adenocarcinoma cell line LoVo to generate L-cell transfectants and a bacteriophage  $\lambda$ gt11 cDNA clone that expressed epitopes of carcinoembryonic antigen. The authors

observed antigen amplification in some secondary transfectants, and concluded that increased cell surface expression of the transfectant antigen resulted from a quantitative increase in gene copy number.

None of the listed publications that precede the priority date of the present application describe or suggest, alone or in combination, a method for achieving expression of a desired mammalian protein in which regulatory elements are inserted, using homologous recombination, in the vicinity of a target gene present in a cell which encodes the protein and is present in the primary host cell.

Copies:

Copies of items AD through AK were previously submitted with the Information Disclosure Statement for U.S. Patent Application Serial Number 07/787,390. Copies of items AA, AB, AC, AL, and AM listed on PTO-1449 are enclosed.

Respectfully submitted,  
SKOULTCHI et. al, Applicants

By: SaraLynn Mandel  
SaraLynn Mandel  
Reg. No. 31,853

Cell Genesys, Inc.  
322 Lakeside Drive  
Foster City, California 94404  
(415) 358-9600 ext. 345  
Enc: PTO Form 1449 and copies of cited publications.